Exhibit J

Tagamet®-Induced Acute Dystonia

A [illegible]-year-old woman presented with an idiopathic acute dystonic reaction after only five doses of cimetidine (Tagamet®). The patient was on no other medications with the exception of oral contraceptives. Emergency administration of IV diphenhydramine HCl brought rapid reversal of this acute dystonic reaction without any neurological sequelae. To our knowledge, this is the first reported case of an acute dystonic reaction associated with cimetidine. [Romisher S, Felter R, Dougherty J: Tagamet®-induced acute dystonia. *Ann Emerg Med* October 1987;16:1162-1164.]

Stephen Romisher, DO, FACEP*
Robert Felter, MD, FAAP†
James Dougherty, MD, FACEP*
Akron, Ohio

From the Department of Emergency Medicine, Akron General Medical Center,* and the Division of Emergency Health Services, Children's Hospital Medical Center of Akron,† Akron, Ohio.

Received for publication [illegible], 1987. Accepted for publication [illegible], 1987.

Address for reprints: Stephen Romisher, DO, Department of Emergency Medicine, Akron General Medical Center, 400 Wabash Avenue, Akron, Ohio 44307.

300 mg [illegible]

INTRODUCTION

Since cimetidine was introduced, there have been numerous reports of neurologic side effects associated with its use.[1-?]

We report a case of cimetidine-associated acute dystonia in a patient after only [illegible] hours of therapy.

CASE REPORT

A [illegible]-year-old woman was seen because of severe right-sided mandibular pain, [illegible] trismus, and dysphasia.

The patient had been placed on ranitidine (Zantac®) 150 mg twice daily one week earlier because of suspected peptic ulcer disease. After two days of therapy her physician discontinued the medication because she complained of intolerable gastrointestinal upset. Two days later, cimetidine (Tagamet®) 300 mg qid was started. The patient took the fifth dose 12 hours prior to admission. Approximately nine hours prior to admission, she noticed the sudden onset of right-sided mandibular pain. Several hours prior to admission she developed right-sided trismus with associated dysphasia. When walking, there was involuntary turning in of her right foot.

The medical history was significant only for a patent foramen ovale that was corrected surgically in childhood. Medications included oral contraceptives for more than one year and cimetidine. The patient denied the use of any other prescription or nonprescription medication or the use of illicit drugs. In addition, she denied mandibular trauma, fever, chills, or symptoms suggestive of pharyngeal pathology.

On physical examination, the patient's vital signs were as follows: pulse, 88; respirations, 18; blood pressure, 118/88 mm Hg; and temperature, 37.1 C. She was alert and oriented with impairment in phonation. There was marked spasm and pain of the right-sided masticatory muscles with deviation of the mandible to the right. The uvula was also deviated to the right, and there were tongue fasciculations. No lingual movements or dysphagia were noted. Pupils were equal and reactive, and extraocular muscles were normal without any evidence of oculogyric dysfunction. The neck was supple without bruits or thyromegaly. Cardiac examination revealed a regular rhythm with a split first heart sound. Right ankle inversion with "pes cavus" deformity was present despite normal reflexes with absent clonus in all four extremities. Gait testing revealed difficulty in ambulation because of an inverted right ankle. The remainder of the physical examination was normal.

A blood sample for phenothiazines was obtained. A peripheral IV line of 5% dextrose and ½ normal saline was placed and she was given 50 mg of diphenhydramine HCl IV with immediate relaxation of the right-sided mas-

dex of examination. There was marked improvement in pantothen. The uvula remained deviated to the right but there were no longer any tongue fasciculations. The right arch showed decent motility in tandem motion. No neurological abnormalities were found and gait testing was normal.

The patient was observed in the emergency department for approximately 90 minutes and discharged home with instructions to discontinue clonidine and commence oral diphenhydramine HCl 50 mg four times per day for 48 hours. We recommend the patient in 24 and 48 hours after his initial presentation. Complete return of normal speech and tick cranial nerve function were noted. The uvula was in the mid-position and was no longer deviated.

Home sterile chloride away no phenothiazides done no admission was required.

DISCUSSION

Acute dystonia is an extrapyramidal side effect (EPS) of antipsychotic medications and related compounds characterized by sudden, involuntary, sustained spasms of a muscle or group of muscles.[1,2]

Any voluntary muscle group may be involved, but those of the head and neck are most frequently involved in adults.

Acute dystonias and dyskinesias are the least frequent but most dramatic forms of EPS.[3] However, dystonic reactions are commonly reported with increasing frequency when associated with neuroleptic use; rates may approach 50%.[4] Symptoms arise suddenly and may be frightening to the patient and observer.

Drugs that affect the dopamine-mediated neurons in the basal ganglia have been implicated in producing EPS. The drugs most notably responsible include neuroleptic agents used to treat psychosis, anticonvulsants such as carbamazepine and gabapentin, parkinsonian and the antiemetics agent metoclopramide.[1,2,5] However, such other drugs as phenylbutazone,[6] ibuprofen,[7] fenoldopam,[8] L-Dopa,[9] and ketamine[10] have been reported.[11]

The possibility of an acute dystonic reaction increases with increasing dosage and frequency but can occur after a single dose. Caldwell and co-workers[12] believe the reactions are idiosyncratic in nature. Acute dystonic reactions usually occurs within 24 to 72 hours of the first dose or after an increase in the maintenance dose.[13]

Clonidine is a histamine receptor antagonist that is its structural analogue of histamine used in the treatment of peptic ulcer disease. The drug has no known effect on central dopaminergic pathways. CNS reactions have been reported with cimetidine therapy and are reversible on discontinuing the medication.[14] Predisposing factors to the development of this side effect include: older age,[15] renal and hepatic impairment,[16] high dose medication,[17] pre-existing psychiatric illness,[18] and simultaneous treatment with psychoactive medication.[19]

Only the previous case of extrapyramidal symptoms has been reported and was associated with cerebral syndrome.[20] These symptoms occurred in a 74-year-old man follow and a 1 g per day dose for 18 days. Renal and hepatic impairment were absent. However, the patient had pre-existing cerebral vascular disease and dementia, and it was difficult to determine if cimetidine was the cause or the reaction. The patient had had previous acute extrapyramidal states.

Our patient was in excellent health with no predisposing factors in the development of acute dystonia or trismus. She had no history of neurologic or psychotic illnesses. Infectious etiologies were not apparent. Toxicological screen was not obtained on other exogenous agents that might cause an acute dystonic reaction because of the inability of the patient's history. She was on no other medications that would confound the possibility of an acute dystonic reaction the safety is unwelcome. Finally, there was an adequate "wash out" period between the time she discontinued ranitidine and began cimetidine.

Emergency treatment is acute dystonia usually discontinuing the suspected offending agent and anticholinergic medication to relieve symptoms immediate. Parenteral diphenhydramine HCl is particularly popular as the drug of choice.[21] However, any anticholinergic agent is appropriate if diphenhydramine was not used.[22]

The emergency administration of diphenhydramine HCl 50 mg IM or slow IV push is one of the treatments of choice in adults.[23] Benztropine mesylate may be given as an alternative to the treatment of choice.[24] Some of quicker recovery than with less drawbacks when compared to diphenhydramine HCl. However, benztropine may on occur if given in IV. However, the exact dose in children has not been fully documented.[25]

Despite the relatively rapid and dramatic recovery with these agents there may be recurrences. To prevent them, Clerc[26] recommends reducing the patient's dose on oral anticonvulsants 50 mg three to four times daily for up to 3 months.

SUMMARY

We present a case of an acute extrapyramidal side effects associated with cimetidine. The presenting symptomatology was typical of EPS as other pyramidal causes of EPS such as drugs or underlying medical problems were not present. While certainly not occurring frequently in patients treated with cimetidine, it should be considered in the differential diagnosis and patient prescribing with an acute dystonic reaction.

The authors thank for their help in the preparation of this article Zeller, MD for technical assistance in this case.

REFERENCES

1. [illegible] Medical Association, [illegible]

2. Kozobolis VP, Rosenberg N, Sotiropoulos N, et al. Neuroleptic and prochlorperazine induced acute dystonic reactions in the emergency department. [illegible]

3. Chase MA. Comparison of [illegible] follow-up days and make [illegible] Med 1981;10:1-11.

4. Schmidt ML, Rosved RH, Jensen OA, et al. Cimetidine. Does it cause acute renal failure in three cases. J Toxicol Clin Toxicol 1982;19:1-5.

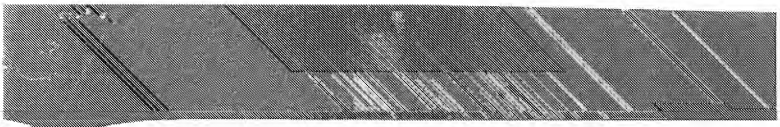
5. Hassan R, Bogaerts G, Saerens B, et al. The effects of cimetidine treatment on renal function in patients with renal failure. Nephron 1980;26:39-43.

6. Thie JF. Cimetidine-induced [illegible] of phenytoin toxicity. [illegible]

7. Stewart CL, Reed JF. Report of [illegible] pharmacokinetic interaction of [illegible] cimetidine concerned with [illegible] Toxicol Appl Pharmacol 1980;56:[illegible]

8. Gomez I, Sanchez FJ, [illegible] Cimetidine in chronic [illegible] Gastroenterology 1980;78:[illegible]

9. Rock KR. Acute dystonic [illegible] Am J Emerg Med 1984;2:[illegible]



[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]